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ORIGINAL RESEARCH

Bilirubin Elevation During Hospitalization Post Radiofrequency Catheter Ablation of Persistent Atrial Fibrillation: Variation Trend, Related Factors, and Relevance to 1-Year Recurrence

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Background: The role of total bilirubin (TBIL) in cardiovascular disease has been increasingly recognized in recent decades. Studies have shown a correlation between total bilirubin levels and the prognosis of patients after heart surgery. This study aimed to investigate the clinical significance of bilirubin elevation in persistent atrial fibrillation (PAF) patients who received radiofrequency catheter ablation (RFCA).

Methods and Results: A total of 184 patients with PAF who received RFCA were retrospectively studied. Laboratory examinations and demographic data were analyzed to identify independent predictors of TBIL elevation. The relationship between TBIL and prognosis was further investigated. Our results indicated that TBIL increased significantly after RFCA. Multiple linear regression analysis showed that TBIL elevation owned a negative correlation with the percentile of low voltage areas (LVAs) in left atria (β=−0.490, P<0.001). In contrast, a positive correlation was observed with the white blood cell (WBC) ratio (β=0.153, P=0.042) and left atrial diameter (LAD) (β=0.232, P=0.025). It was found that postoperative TBIL levels increased and then gradually decreased to baseline within 5 days without intervention. The bilirubin ratio <1.211 indicated the possibility of 1-year AF recurrence after ablation with a predictive value of 0.743 (specificity = 75.00%, sensitivity = 66.67%).

Conclusion: Bilirubin elevation post PAF RFCA was a common phenomenon and was associated with 1-year recurrence of AF in PAF patients after RFCA.

Keywords: bilirubin, atrial fibrillation, radiofrequency catheter ablation, oxidative stress, prognosis

Introduction

Bilirubin is the catabolite of hemoglobin and myoglobin and is conjugated to glucuronic acid by the UDP-glucuronosyltransferase enzyme in the liver, causing it to be excreted in bile.[1] It is widely identified as a significant indicator of liver damage. In recent decades, bilirubin has been recognized as an essential endogenous anti-inflammatory and antioxidant molecule, which can affect atherosclerosis through various inhibitory mechanisms, including LDL oxidation, vascular smooth muscle cell proliferation, and endothelial dysfunction.[2–4] Research conducted in recent years has revealed that the serum level of total bilirubin was associated with the prognosis in coronary artery disease patients.[5,6] In addition, a previous cohort study has suggested total bilirubin (TBIL) could act as an effective and inexpensive auxiliary predictor in new-onset non-ST elevation myocardial infarction (NSTEMI).[7]

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Atrial fibrillation (AF), the most common arrhythmia in the elderly, can be classified as paroxysmal (lasting <7 days) and persistent (lasting >7 days). Its incidence increases with age and is associated with reduced quality of life.[8] There are about 37.574 billion cases of atrial fibrillation worldwide (0.51% of the world's population). With the use of anticoagulation drug, the incidence of recurrent ischemic stroke and systemic embolism induced by atrial fibrillation has been greatly decreased.[9] Gratifyingly, radiofrequency catheter ablation (RFCA) for AF has emerged as a more promising and effective treatment that offers the possibility of a cure.[10–13] The AHA/ACC/HRS guidelines suggest RFCA as a first-line treatment for patients with symptomatic AF.[14]

We recently observed an elevated trend of TBIL in patients with persistent AF (PAF) after RFCA. Previous studies have suggested that transient hyperbilirubinemia or jaundice could occur after cardiovascular surgery, which was associated with higher early mortality.[15–17] It was an essential indicator of prognosis. Reports on the influencing factors and prognostic significance of bilirubin in PAF patients after RFCA are scarce. This study aims to investigate possible factors influencing changes in serum TBIL as well as the potential association between increased TBIL and prognosis after ablation of PAF.

Materials and Methods

Data Source and Population Selection Criteria

Between May 2020 and March 2022, a total of 184 patients with PAF who underwent RFCA in our hospital were enrolled for this retrospective study, excluding the following patients: 1. Underwent cryoballoon catheter ablation (CRYO) or atrioventricular node ablation combined with pacemaker implantation; 2. The subjects without baseline serum TBIL, TBIL level within 48 hours after ablation, or TBL level before discharge; 3. Patients with severe liver or kidney dysfunction (Child-Pugh classification grade B and above or CKD stage 4 and above) could not tolerate surgery. 4. Patients with less than a year of follow-up after discharge. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University and was performed in compliance with the Helsinki Declaration. All patients had signed written informed consent forms.

Data Extraction

For all the included participants in this study, demographic data including age, sex, body mass index (BMI), smoke status, alcohol use, hypertension, diabetes mellitus, heart failure, and coronary artery disease were retrospectively collected. Furthermore, laboratory examinations including bilirubin, white blood cell (WBC), hemoglobin (HB), blood platelet (PLT), alanine transaminase (ALT), serum creatinine (SCR), blood urea nitrogen (BUN), and hemoglobin A1C (HbA1c) were recorded. Blood cell counts were tested with BC-7500 Fully Auto Hematology Analyzer (Mindray). ALT, BUN, and SCR levels were measured with AU5800 Full-automatic biochemical analyzer (Beckman). HbA1c level was determined with D-100 Hemoglobin Testing System (Bio-Rad). Left atrial diameter (LAD), left ventricle ejection fraction (LVEF), and the percentage of low voltage areas (LVAs) in the left atria were also collected. LAD was assessed by anteroposterior dimension on 2D echocardiography in the parasternal long axis view. Left end-diastolic diameter and end systolic diameter were measured under the same view to quantify the LVEF. Left atria voltage was mapped during the RFCA procedure. The areas of voltage less than 0.5mV were defined as LVAs, and the percentage of LVAs was calculated by dividing LVAs by the mapped left atrium area. If the patient had undergone multiple laboratory tests during hospitalization, only the test results of the initial and within the first 48 hours post-procedure were used for analysis. For TBIL, we gathered data on TBIL levels from patients at three time-points: initial, within 48 hours after ablation, and 5 days after RFCA for further analysis. The 1-year recurrence of AF post procedure was collected based on outpatient follow-up recording. To better investigate the relationship between the indicators, we used the ratio of each laboratory indicator for statistical analysis. The ratio of laboratory data in this study was defined as the ratio of post-RFCA to pre-RFCA.

Radiofrequency Catheter Ablation

RFCA was performed under fluoroscopy guidance and a 3-dimensional mapping system (CARTO; Biosense Webster, Diamond Bar, CA, USA). Before ablation, left atrium voltage mapping was performed to evaluate the substrate of the left

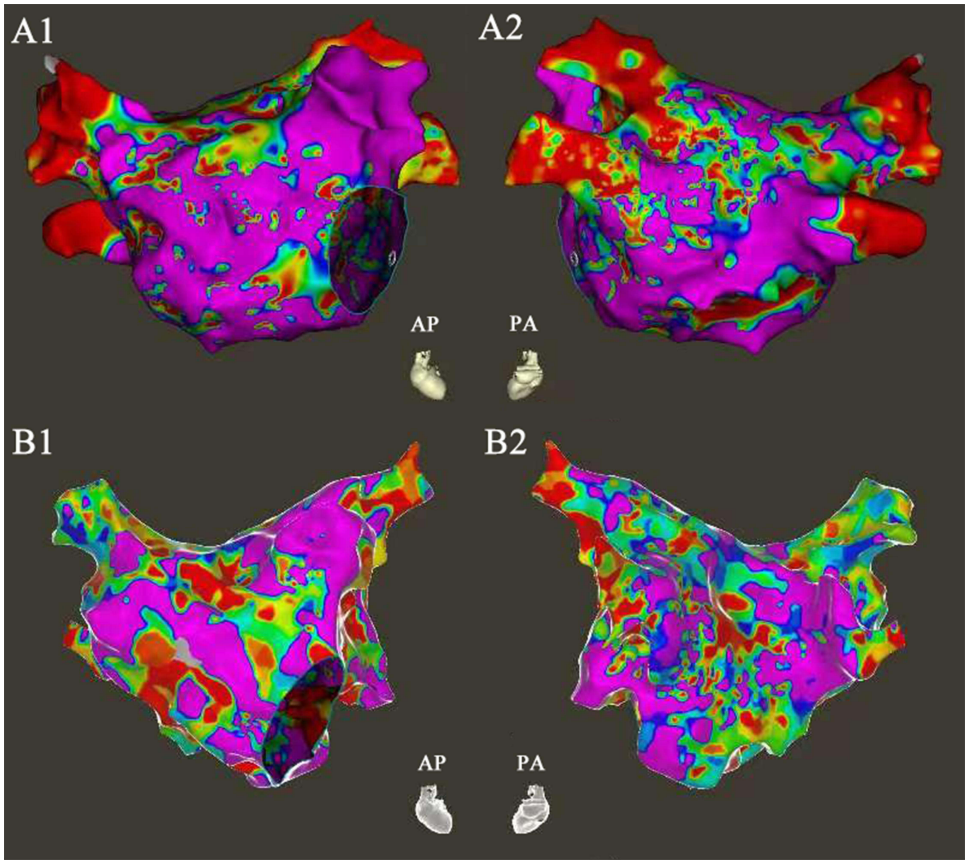

Figure 1 Left atrial (LA) voltage mapping from 2 patients. The area of voltage <0.5 mV was used to define scar tissue (<0.5 mV – red, green, and blue on the map) and normal tissue (>0.5 mV – purple on the map). A1 and B1 were in the anteroposterior (AP) projection. A2 and B2 were in the posteroanterior (PA) projection. Patient 1 (A1-A2) had better substrate in LA, and the LVA (30.6%) was limited. Patient 2 (B1-B2) had widespread LVA (79.2%).

atrium in AF rhythm (Figure 1). The bilateral PVs antrum was circumferentially ablated in all patients, and additional linear ablation, including the anterior wall line, roof line, and posterior line, was continued unless AF had been converted into sinus rhythm. Radiofrequency energy was delivered with a maximum temperature of 43°C, preset power of 35–50w, a flow rate of 17mL/min, targeting ablation index (AI) value of 450 at anterior left atrial (LA) aspect, 400 at superior and inferior LA aspect, 380 at posterior LA aspect. Biphasic external cardioversion was used to restore sinus rhythm if AF was still present after ablation.

Post-Ablation Management and Follow-Up

All patients were discharged with anticoagulant drugs routinely for at least three months after ablation and were restarted with antiarrhythmic drugs if recurrent AF was detected. A 12-lead electrocardiogram (ECG) was routinely obtained at each clinic visit, and 24-hour Holter monitoring was undertaken at 3, 6, and 12 months. AF recurrence was defined as a documented AF lasting >30s on ECG or Holter 3 months after the procedure.

Statistic

Categorical variables are presented as numbers and percentages. Continuous variables are presented as the mean ± SD or the median with interquartile range (IQR) if the data is a non-normal distribution. Student's *t*-test analyzed Gaussian data, and nonparametric tests were used for non-Gaussian data. We used multiple linear regression analysis to identify the independent predictors of bilirubin change. The cutoff for total bilirubin was determined by receiver operating characteristic (ROC) curves. All statistical analyses were conducted using SPSS version 26.0 (IBM, Armonk, New York, USA), and $P < 0.050$ was considered statistically significant.

Results

Baseline Characteristics

A total of 184 patients (135 males; mean age 65.56 ± 10.65 years) with PAF met the study inclusion and exclusion criteria. The average in-hospital day was 6.19 ±0.976 days. Demographic data, pre-post procedure laboratory data, and the ratio of these data are shown in Table 1. We found that items including WBC, HB, PLT, ALT, TBIL, SCR, and BUN showed significant changes between pre- and post-procedure ($p<0.01$).

Changes in Bilirubin

Boxplots were created to represent three time-points bilirubin visually (Figure 2) and we compared TBIL among these points. The graphical representation illustrates a notable increase in bilirubin levels for most patients after RFCA, followed by a decline to basal level within 5 days after the procedure without intervention. The results showed that the TBIL level within 48 hours after RFCA significantly differed from that of the initial and 5 days after RFCA ($P < 0.05$). However, there was no significant difference between the initial and 5 days after RFCA ($P > 0.05$).

The Association Between the Ratio of Bilirubin and Different Variables in AF Patients by Multivariate Analysis

Age, HbA1c, the ratio of WBC, HB, PLT, SCR, BUN, ALT, the LAD, and the Percentage of LVAs were used to find the factor that correlates with the ratio of bilirubin (Table 2). Our findings revealed a significant negative correlation between the percentage of LVAs and the ratio of bilirubin ($\beta=-0.490$, $P<0.001$). On the other hand, LAD ($\beta=0.232$, $P=0.025$) and the ratio of WBC were positively correlated with the bilirubin ratio ($\beta=0.153$, $P=0.042$). These correlations shed light on

Table 1 Demographic and Clinical Characteristics of Patients [n (%), $\overline{X}\pm S$]

	Pre-Procedure (Initial) Data	Post-Procedure Data	The Ratio of Data*	*P* value
Age (years)	65.56±10.65	/	/	/
Male	135 (73.37)	/	/	/
Body mass index (kg/m^2)	24.88±3.27	/	/	/
Average in-hospital day (days)	6.19±0.976			
Hypertension	95 (51.63)	/	/	/
Diabetes	24 (13.04)	/	/	/
Heart failure	4 (2.17)	/	/	/
Coronary artery disease	16 (8.70)	/	/	/
Drinking	45 (24.46)	/	/	/
Smoking	48 (26.09)	/	/	/
Glycosylated hemoglobin (%)	5.94±0.76	/	/	/
LAD (mm)	42.06±5.65	/	/	/
LVEF (%)	62.16±10.16	/	/	/
Time of operation (min)	161.92±42.98	/	/	/
Percent of LVAs (%)	33.3±6.685			
WBC (10^9/L)	6.59±1.87	8.90±2.76	1.40±0.46	<0.01
HB (g/L)	141.08±17.16	128.79±16.13	0.91±0.06	<0.01
PLT (10^9/L)	209.72±56.91	178.30±50.16	0.86±0.11	<0.01
ALT (U/L)	31.02±28.60	33.72±31.36	1.22±0.53	<0.01
TBIL (μmol/L)	15.96±9.42	23.90±13.80	1.58±0.64	<0.01
SCR (μmol/L)	81.66±26.47	70.57±21.04	0.88±0.12	<0.01
BUN (mmol/L)	6.87±2.12	6.00±1.67	0.90±0.19	<0.01

Notes: *= postoperative data divided by preoperative data. Correlation test of preoperative and postoperative data. Quoted for the analysis of paired samples *T*-test or Wilcoxon rank sum test for continuous or categorical variables, respectively.

Abbreviations: LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVAs, low voltage areas; WBC, white blood cell; HB, hemoglobin; PLT, platelets; ALT, alanine aminotransferase; TBIL, total bilirubin; SCR, serum creatinine; BUN, blood urea nitrogen.

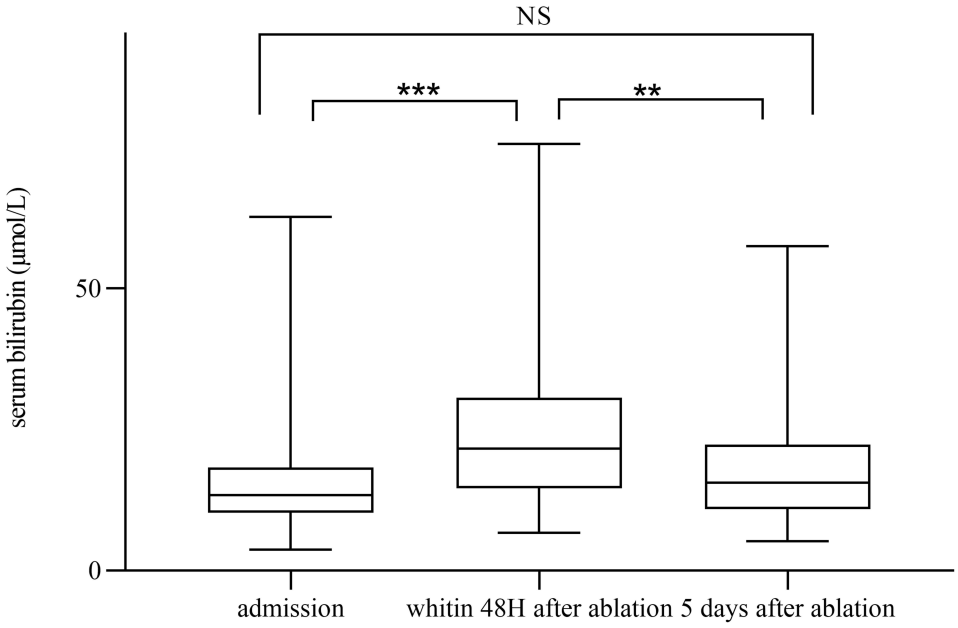

Figure 2 Change trend of bilirubin before and after RFCA.
Notes: ***=P < 0.001, **=P < 0.01.
Abbreviation: NS, no statistical difference.

the potential influence of these factors on bilirubin levels and provide valuable insights into the mechanism of bilirubin change after ablation.

The Correlation Between Bilirubin Ratio and Recurrence Rate

According to the bilirubin ratio, we divided the patients into two groups for further analysis. Overall, 92 patients were in the low bilirubin ratio group (bilirubin ratio < 1.43), and 92 patients were in the high bilirubin ratio group (bilirubin ratio ≥1.43). Intriguingly, our investigation revealed a notable reduction in the rate of AF recurrence in the high bilirubin ratio group, as illustrated in Table 3. This finding indicates a potential association between the bilirubin ratio and AF

Table 2 Multiple Linear Regression Analysis of Total Bilirubin Levels in AF Patients

	Beta	t	*P* value
Age	−0.043	−0.560	0.576
HbA1c	0.074	0.989	0.324
Ratio of WBC	0.153	2.047	0.042
Ratio of HB	0.034	0.451	0.653
Ratio of PLT	−0.109	−1.439	0.152
Ratio of ALT	0.052	0.685	0.494
Ratio of SCR	−0.087	−1.169	0.244
Ratio of BUN	−0.024	−0.324	0.746
LAD	0.232	2.256	0.025
Percent of LVAs	−0.490	−4.783	<0.001

Abbreviations: HbA1c, hemoglobin A1C; WBC, white blood cell; HB, hemoglobin; PLT, platelets; ALT, alanine aminotransferase; SCR, serum creatinine; BUN, blood urea nitrogen; LAD, left atrial diameter; LVAs, low voltage areas.

Table 3 Recurrence of Atrial Fibrillation in the Two Bilirubin Ratio Groups

Long-Term Prognosis	The Ratio of Bilirubin	
	<1.43 (n=92)	≥1.43 (n=92)
Relapse	37	11
Sinus rhythm maintenance	55	81
Recurrence rate	0.40	0.12

recurrence, suggesting that patients with higher bilirubin ratios may experience a lower likelihood of AF recurrence following the ablation.

ROC Curves of the Ratio of Total Bilirubin to Predict AF Recurrence

The cutoff value for the total bilirubin level that could predict AF recurrence was determined by analyzing the ROC curve. As shown in Figure 3, the area under the curve (AUC) was 0.743 (specificity = 75.00%, sensitivity = 66.67%). The above data analysis showed that the bilirubin ratio <1.211 was a good differential index predicting the recurrence of AF after catheter ablation.

Discussion

In patients with PAF undergoing catheter ablation, there was a significant elevation of bilirubin in the first two days after the procedure, which was a common phenomenon, and could subside to baseline within five days without any special treatment. Higher bilirubin post-ablation was associated with a lower rate of 1-year recurrence of AF. The bilirubin ratio <1.211 indicated the possibility of AF recurrence post-catheter ablation with a relatively good predictive value. Our study demonstrated that bilirubin, a blood serum marker commonly used and easily obtained in clinics, could potentially predict clinical outcomes of catheter ablation for PAF.

Bilirubin elevation post-cardiovascular surgery or in cardiovascular incidents is not a rare phenomenon. However, it is controversial.[3,5,15,17–19] Recent studies suggested that postoperative bilirubin elevation was associated with increased postoperative ventilation requirements and liver dysfunction, causing reduced long-term survival rate, recognized as a cost-effective prognostic marker of adverse outcomes.[15,16] On the contrary, other studies implied bilirubin elevation had

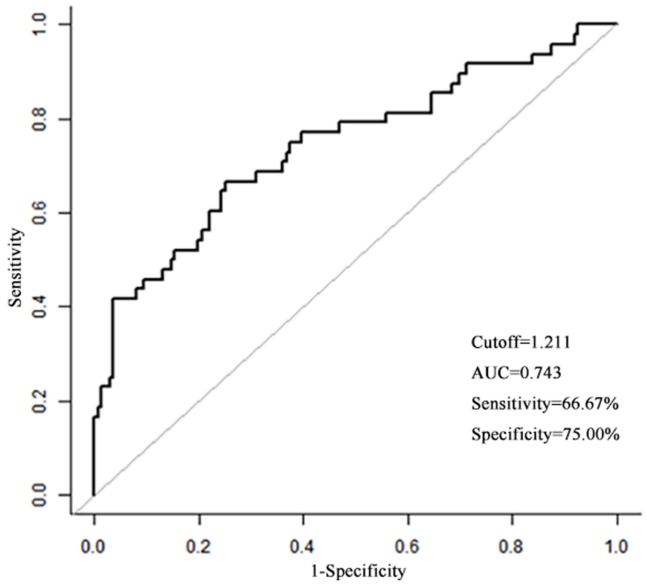

Figure 3 The cutoff for the ratio of total bilirubin to predict atrial fibrillation recurrence by receiver operating characteristic (ROC) analysis.

a protective role in cardiovascular diseases; an inverse association between circulating total bilirubin level and CVD risk was detected independent of established risk factors.[20–23] In our study, an acute elevation of bilirubin (range 15.96±9.42 umol/L from 23.90±13.80 umol/L) was commonly observed post-AF catheter ablation. By one-year follow-up, intriguingly, we found that acute elevation of bilirubin predicted a low one-year recurrence.

The potential mechanisms underlying the bilirubin elevation were speculated. Bilirubin results from heme breakdown and derives from two main sources, 80% of which is made from the breakdown of hemoglobin in senescent red blood cells, while the remainder originates from the turnover of various heme-containing proteins. Of note, our study found that the elevation of bilirubin was not associated with the decrease in hemoglobin. Thus, it was reasonable to infer that the bilirubin mainly came from the other heme-containing proteins. It has been proven there was a myocardial injury during RFCA with myoglobin elevation.[24,25] induced damage of the membrane of cardiomyocytes and leakage of myoglobin. The ablation energy delivered to the atrium inducing damage of the membrane of cardiomyocytes and leakage of myoglobin. In addition, previous studies reported catheter ablation could render a series of oxidative responses, combined with elevation of inflammatory factors, catalase, peroxidase, and so on.[26,27] The breakdown of heme molecules, such as myoglobin, catalase, and peroxidase resulted in the production of the catabolic product, bilirubin.[25,26,28]

The study suggested that the ratio of bilirubin elevation correlated negatively with the percentage of LVAs and positively with the ratio of WBC and left atrium size. A previous study once proposed that troponin T level may be reflective of the preservation of healthy LA myocardium at the time of catheter ablation of atrial fibrillation.[24–26] Thus, a higher elevation of troponin T was observed in a good substrate left atrium. Myoglobin was a biomarker similar to troponin T. Clinical studies revealed that the low voltage area in PAF frequently correlated positively with the scar and fibrosis of the left atrium and indicated a bad substrate.[29,30] It was reasonable to infer that the more fibrotic scarring in the atrium, the less viable cardiomyocytes, and the less damage to cardiomyocytes during ablation, results in less release of myoglobin during ablation, leading to a lower elevation of bilirubin. An enlarged LA is considered to indicate more significant fibrotic scarring in the atrium. However, in this study, bilirubin was positively correlated with LAD, possibly due to the fact that patients with larger atria tended to have a more extensive ablation range, collectively causing more damaged cardiomyocytes. As for the extent of bilirubin elevation correlating positively with the WBC, previous research revealed that circulating white blood cells may reflect oxidative stress and amplify oxidative stress in cardiovascular diseases. We speculated that a higher level of oxidative stress, in turn, promotes the elevation of bilirubin.[31]

Why the elevation of bilirubin could predict 1-year AF recurrence post-catheter ablation was also speculated. As mentioned above, a more significant elevation of bilirubin post-catheter ablation may indicate a good substrate of the left atrium. Many studies have revealed that left atrium substrates are independent predictors of recurrence after ablation. Taken together, we proposed that bilirubin level could be a potential biomarker to predict 1-year recurrence of AF post-catheter ablation.

Study limitation: Firstly, the data were retrospectively collected, such as bilirubin level, which was measured at specific times in this study, but were not continuously monitored every day during hospitalization, which may cause time effect bias. We suggest a prospective study to further testify to our findings, by continuously monitoring bilirubin fluctuations. Secondly, our study did not measure myoglobin, catalase, or peroxidase biomarkers. However, the quick metabolism of these molecules made the continuous observation of these molecules infeasible. Thirdly, the left atrium size was evaluated by left atrium diameter, which is, to some extent, inferior to the parameters like left atrium volume index.[32] We expect a prospective study in the future to adopt the left atrium volume index instead.

Conclusion

In patients with persistent AF undergoing catheter ablation, elevation of bilirubin was a common phenomenon, which could subside to baseline without treatment. The elevation of bilirubin may reflect the substrate of the left atrium and oxidative stress at the time of ablation. Post-RFCA, TBIL elevation was associated with clinical outcomes in patients with persistent AF. A higher degree of TBIL elevation indicated a lower possibility of 1-year recurrence of AF, which may be a predictor of clinical outcome of catheter ablation for persistent AF.

Data Sharing Statement

The deidentified participant data will not be shared.

Ethics Approval

This study was approved by the Institutional Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University (Approval no.2022-K-273-01).

Consent for Publication

No information or images that could lead to the identification of a study participant were mentioned in our study.

Author Contributions

All authors made significant contributions to conception, study design, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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